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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/390,634	09/07/1999	PAUL J. PRICE	0942.4190002	7270

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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W., SUITE 600
WASHINGTON, DC 20005-3934

EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	24

DATE MAILED: 06/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Advisory Action

Application No.	Applicant(s)
09/390,634	Price, P
Examiner	**Art Unit**
Joseph T. Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Jun 12, 2002* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attached.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: *89-126*

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

10. ☐ Other:

Deborah Crouch
DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630

Section 5(c):

Applicant summarizes the basis of the rejection outlining four general points raised as issues regarding enablement, and argue each in turn.

(A) The existence of stem cells from other species: Applicant argues that embryonic stem cells as used in the present specification is not limited to totipotent cells. Further, even in the absence of such cells the evidence for lack of enablement requires more that a lack of positive evidence. See pages 4-6. (B) The level of predictability for isolating and producing ES cell lines: Applicant reviews the references relied upon in the basis of the rejection and argue that there is no evidence that isolating ES cells is "highly unpredictable". See pages 6-8. (C) The ability to extrapolate conditions: Applicant argues that in order to show a *prima facie* case of enablement, demonstrating a difference in making a particular cell type is not sufficient point to *In re Wands*. In addition, Applicant has supplied several post-filing references teaching the culturing of ES cells with the commercially available KnockOut SR serum replacement. See pages 8-12 and attachments. (D) The inclusion of numerous permutations: Applicants argue that trying the multiple formulations encompassed by the claims would not be undue and is routine in the art. See pages 12-14. Applicant's arguments have been fully considered, but not found persuasive.

Initially, it is noted that the specification defines ES cells as 'established cell lines derived from the inner cell mass of a blastocyst. The undifferentiated cells are pluripotent and take part in the formation of *all* tissues, *including the germ line*." (emphasis added, specification page 1; lines 8-9). Though the specification recites pluripotent, the ability to contribute to the germ line

is a property of a totipotent cell. The examination of the instant claims has been directed to the embodiments encompassed by this cell. A review of the present specification does not indicate that embryonic stem-like cells that are not totipotent were contemplated. In addition, this is further supported in the methods of use for generating transgenic animals.

Examiner would agree that a lack of evidence is not sufficient alone for the basis of lack of enablement, however in this specific circumstance the absence of ES cells clearly indicates the necessity for detailed guidance and the unpredictability of the art for deriving and culturing ES cells. The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In the instant case, Examiner has provided a review of the state of the art for embryonic stem cells to establish that though mouse ES cells have been made and cultured, the cells from other species have not been isolated because the methods required are not simple extensions of those used in mice. This establishes that at the time of filing that the artisan was trying to establish ES cells from other species, however all attempts to adapt what was known in the art failed to produce an ES cell from another species, and that such cells did not exist. Though the post filing art teaches that human totipotent ES cells may now exist, the behavior and requirements of these human ES cells are different from those of mouse ES cells. This difference between the cells was not predicted in

the art, and further supports and serves to demonstrate the unpredictability of the art and the necessity for detailed guidance for each particular species.

The instant claims are very broad encompassing a method for expanding embryonic stem cells in the absence of serum (*i.e.* no requirement of the addition of specific factors) and compositions used in said method. Dependent claims recite specific factors which are used or added to the media, however no specific amounts are indicated. The specification provides general guidance on what factors one can add to the media. The specification also provides working examples for a few media conditions and mouse ES cells. A review of the references submitted with the instant amendment some of the references teach that ES cells can be cultured in the absence of serum (though some methods use serum). However, an apparent requirement is the serum supplement, KnockOut SR. The specific nature and composition of the serum supplement is not disclosed in any of the references so it is difficult to assess whether the examples provided by these references are supported by the present disclosure. A narrow interpretation would conclude that the cells are cultured without serum, however the references when viewed as whole clearly teach that a serum supplement is used. The present specification sets forth a general need and motivation for defining a completely defined culturing condition absent the need of serum free for culturing ES cells. However, the specification fails to provide the necessary detailed guidance for ES cells from species other than the mouse. In the basis of the rejection, it has been established that at the time of filing the skilled artisan recognized differences among ES cells and that conditions for one species was not adaptable to another

species. Examiner would agree that it is routine to optimize culturing conditions when working conditions are known, however in view of the unpredictability and the teaching of the art that conditions for even the isolation of ES cells could not simply be adapted, there is no expectation that the methods of culturing would not also be unique. Further, post filing art clearly teaches that the culturing requirements are different. In view of the unpredictability of art and the generality of the guidance in the present disclosure, the multitude of possible various conditions would be considered undue because they represent experiments beyond simple optimization, and represent a broad invitation to try without any real expectation of success.

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel*. Enablement has been considered in view of all of the Wands factors. In view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to ES cells of any species, and the general unpredictable state of the art with respect to the generation of ES cells of all species, it would have required undue experimentation for one skilled in the art to make and/or use the claimed inventions as broadly claimed.